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**Use of synthetic grafts in pelvic reconstruction: A path of continued discovery**

Cohen SA *et al*. Grafts in pelvic reconstruction, continued discovery

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**Abstract**

Since the 1990s, mesh has been used in pelvic reconstruction to augment repairs for stress urinary incontinence and pelvic organ prolapse (POP). In 2008 and 2011, the United States Food and Drug Administration (FDA) issued Public Health Notifications ultimately informing providers and the public that complications associated with the use of synthetic mesh in the transvaginal repair of POP are not rare. In this review, we (1) examine literature characterizing surgical practice-patterns subsequent to the FDA announcements; (2) describe presentation of mesh-associated complications and outcomes of management; (3) discuss the most recent materials science research; and (4) seek to characterize whether or not mesh has lived up to the long-term efficacy promise of a permanent implant. Durability of mesh-augmented anatomical outcomes do not consistently translate into improved patient satisfaction and subjective outcomes. This, when coupled with the possibility of mesh-associated complications, emphasizes the need for continued innovation beyond the status quo of current synthetic grafts.

**Key words:** Mesh; Synthetic graft; Mesh-associated complications; Mesh extrusion; Mesh erosion; Pelvic organ prolapse; Host response

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**Core tip:** While mesh-augmented prolapse repair would appear to improve anatomical outcomes, it does not consistently translate into improved patient satisfaction. The use of mesh implantation has to be balanced with the added morbidity of possible delayed mesh-associated complications over-time. We simply seek to recognize that there will be women who will suffer from adverse outcomes after these implants (just as there can be complications after any type of surgery); it is important to recognize the need and possible benefit of effective intervention, all the while continuing to challenge ourselves to improve the techniques and materials we use in pelvic reconstruction.

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**INTRODUCTION**

Mesh was introduced into surgical reconstruction of abdominal hernias in the 1950s; it was not until the 1990s that pelvic surgeons began using mesh to augment repairs for stress urinary incontinence (SUI) and pelvic organ prolapse (POP)[1]. The United States Food and Drug Administration (FDA) issued approval for the marketing of these mesh products for such indications through a 510(k), which is a premarket submission made to the FDA demonstrating that the device in question is at the least as safe and effective as another approved product (which was abdominal mesh in this instance). Synthetic midurethral slings (MUS) composed of polypropylene for SUI, in addition to transvaginal mesh kits devised for use in POP repairs, were introduced through a number of companies in the ensuing decade, with a resultant diffusion of these products. Most physicians were made aware of these new devices and kits through print advertising in professional journals, manufacturers’ hospital sales force, and displays at specialty society meetings[2].

In October 2008 and July 2011, the FDA issued Public Health Notifications ultimately informing providers and the public that “serious complications” associated with the use of synthetic mesh in the transvaginal repair of POP are not rare[3,4]. The most commonly reported complications included vaginal mesh extrusion, mesh contraction associated with vaginal shortening, vaginal tightening, and vaginal pain. The FDA also made clear in this release that the warning was for transvaginal mesh placed for POP and was not inclusive of MUS procedures. In 2012, the FDA required manufacturers of transvaginal mesh POP products and single-incision mini-slings for SUI to conduct postmarket surveillance studies on these devices. In April 2014, the FDA released another update saying it was issuing a proposal to reclassify surgical mesh for transvaginal POP repair from a moderate-risk device (class II) to a high-risk device (class III), requiring manufacturers to submit a premarket approval application for the agency to evaluate safety and effectiveness[5]. In January 2016, this was approved[6].

Khan *et al*[7] has published work evaluating patterns in POP repair using Public Use Files from the Centers for Medicare and Medicaid Services, identifying a 5% random sample of national beneficiaries with diagnosis codes for POP from 1999 through 2009. Procedure codes were used to evaluate non-surgical and surgical management trends in this cohort. After 2005, when codes were made available, mesh/graft repairs were specifically analyzed as well. In any one year in the cohort, they found the number of women with a diagnosis of POP remained stable. There was no significant change in the rates of prolapse repairs over the decade. The study did note a rapid rise in mesh use, with 41% of all women undergoing surgery in 2009 having mesh or graft placed at the time of repair. In efforts to frame the impact of the national climate on mesh use, Clemons *et al*[8] utilized an electronic survey of American Urogynecologic Society (AUGS) members between December 2011 and January 2012, to determine how the 2011 FDA safety update impacted use of synthetic mesh products by pelvic surgeons. Frequency of graft use in POP (including transvaginal and transabdominal approaches) and SUI were queried. 53% (507 of 962 members) responded; before the FDA warning 90% used synthetic mesh and 34% used biologic grafts in POP repair; 99% used synthetic mesh slings for SUI. After the FDA statement update, transvaginal mesh (for POP repair) use decreased by 40%; 12% stopped using it altogether. There was no change in transabdominal mesh POP procedures (*i.e.*, sacrocolpopexy), use of biologics, or synthetic mesh slings. Wang *et al*[9], performed another trend analysis using a 5% Medicare claims database, from 2001 to 2011, identifying POP diagnoses and related procedures with appropriate coding. The rate of mesh use increased dramatically from 2% of repairs in 2005 to 35% by 2008, at which time the initial FDA warning was issued. Subsequent to the FDA warning, the rate of sacrocolpopexy procedures (abdominally-placed mesh, as opposed to transvaginally-placed mesh) almost doubled yearly until 2011.

Anger *et al*[10] examined short-term outcomes between prolapse repairs with and without mesh using the national Medicare beneficiaries data set. Reoperation was higher in the prolapse repair/nonmesh cohort *vs* the prolapse repair/mesh cohort (6%-7% *vs* 4%, *P* < 0.02). The mesh removal rates were higher in the mesh *vs* nonmesh group (4% *vs* 0%-1%, *P* < 0.001). Mesh use was associated with a small decrease in early reoperation for prolapse; it was also associated with more dyspareunia, mesh-related complications, and urinary retention, even when controlling for concomitant sling. When examining the literature for more long-term outcomes, a retrospective review of sacrocolpopexy complications reported by Arsene *et al*[11] found median time between initial surgery and first reoperation was 3.9 ± 5.7 years. In 2013, Nygaard *et al*[12] publish long-term outcome results of the randomized, masked two-year colpopexy and urinary reduction efforts (CARE) trial. At 7 years follow-up, mesh extrusion/erosion probability estimated by Kaplan-Meier method was 10.5% (95%CI: 6.8-16.1), leading the authors to conclude that abdominal sacrocolpopexy effectiveness must be balanced with long-term risks of mesh and/or suture extrusion/erosion. Previous analysis by the same group had concluded that concomitant hysterectomy, smoking, and certain mesh types appear to be modifiable risk factors associated with subsequent mesh complications after sacrocolpopexy[13].

**PRESENTATION AND MANAGEMENT OF MESH-ASSOCIATED COMPLICATIONS**

Mesh-associated adverse events can be viewed within the framework of immediate and late complications. Additionally, the sphere of influence of mesh-associated complications can be further understood in terms of their local, regional, and possibly systemic impacts. Mesh extrusions and erosions (mesh inside the lower urinary or gastrointestinal tract) are examples of adverse outcomes that can actually be either immediate or late complications. Vaginal mesh extrusion occurs secondary to inadequate coverage of vaginal tissue, poor vascularity, early resumption of sexual intercourse, and placement of the mesh within a thin, attenuated vaginal wall[14]. Local signs/symptoms of mesh-associated adverse outcomes can include acute urinary retention, urinary urgency, persistent vaginal bleeding/discharge, vaginal pain/scarring, and dyspareunia (if a male partner reports pain during relations, this has been described as “hispareunia”). Regional complications can include groin pain, leg pain, suprapubic pain, secondary prolapse, and possibly, defecatory dysfunction. In addition, further areas of ongoing research include possible systemic reactions to implanted synthetic mesh products. It should be clearly stated - there is no objective data yet to date to support a connection or etiology that would explain systemic symptoms caused by placement of synthetic mesh. A mechanism for this may or may not be an actual reality. That being said, at our tertiary referral center, approximately 20% of patients presenting with possible mesh-associated adverse outcomes report a constellation of de novo symptoms including but not limited to: intermittent skin rashes, joint pain, myalgias, cough, and/or alopecia.

The management of mesh complications has developed into an emerging field, termed by some “meshology”, with a need for specialized training within Female Pelvic Medicine and Reconstructive Surgery (FPMRS) fellowships[15,16]. Methods for the management of vaginal mesh extrusion are described in the literature, ranging from observation alone, to use of topical estrogen or antiseptics, systemic or topical antibiotics, office-based trimming of the extruded material, and operative excision, at times requiring significant pelvic reconstruction[17]. When counseling patients regarding possible mesh complications, those at increased risk have vaginal atrophy, prior surgery, previous chronic steroid use, auto-immune disorders, or other factors which may mitigate wound healing (Table 1). Tijdink *et al*[18] noted differences in mesh-related symptoms, dependent upon the mesh insertion procedure, with pain and dyspareunia mainly seen after vaginal mesh insertion and vaginal bleeding and discharge after sacrocolpopexy. Protrusion of sling material or banding in the lateral fornices has been described as an etiology of persistent dyspareunia in patients with a MUS placed through the transobturator approach[19]. A retrospective review of 90 patients over a year who underwent retropubic placement of a MUS revealed 4 patients with vaginal extrusion of mesh; 2 patients were asymptomatic, with mesh extrusion identified at routine physical examination 6 wk postoperatively. Two patients had persistent vaginal discharge 6 wk postoperatively, including 1 who complained primarily of partner discomfort during sexual intercourse[20]. Each patient was observed conservatively, without medication or surgical intervention and asked to abstain from sexual intercourse; 3 mo postoperatively all 4 had complete spontaneous epithelialization over the mesh. In a retrospective review of 73 patients who underwent complete and/or partial mesh excisions secondary to mesh-related symptoms subsequent to prolapse or SUI surgery, 63% failed conservative management with estrogen cream, antibiotics, and/or physiotherapy[18]. Literature supports the surgical excision of mesh if 3 mo of conservative treatment has resulted in no improvement or the erosion is more than 1 cm[21].

Multiple groups have reported outcomes of their series regarding mesh removal in the setting mesh complications. In a multicenter, retrospective review, Unger *et al*[22] reported the results of surveys given to 101 women treated for vaginal mesh complications; 51% of women in the study underwent surgical management as treatment, and less than 10 % required a second surgery. Sixty-three percent (19 of 30) of patients with pain prior to intervention reported significant improvement after treatment; however, almost a third reported worsening pain or no change after surgical management. Less than half of patients with voiding dysfunction improved after intervention[22]. In another study, validated instruments were administered to 84 women whom had experienced complications associated with vaginal mesh; each had undergone some type of treatment (surgical intervention, treatment by pelvic pain specialists, or physical therapists)[23]. The study’s mean interval since presentation was 2.3 years. Twenty-two percent of reported vaginal discharge, 15% vaginal bleeding or spotting, and 45% sexual abstinence due to problems related to mesh. Despite 2 years of tertiary care level multidisciplinary treatment, 29% were the same or worse.

Hammett *et al*[24] reported a single-center, 10-year retrospective review of patient satisfaction after surgical excision of mesh, in the setting of mesh-associated complications; a total of 57-patients (including both mid-urethral slings and vaginal mesh for prolapse) were included with a diagnosis of mesh extrusion into the vaginal wall[24]. The International Continence Society (ICS) and International Urogynecological Association (IUGA) classification system was used to describe the mesh complications. The most common presenting patient complaints were chronic pelvic pain (55.9%), dyspareunia (54.4%), and vaginal discharge (30.9%). At a 6-wk post-operative visit, 57.3% of patient’s symptoms were completely resolved and 14.6% were improved. Hokenstad *et al*[25] were able to analyze surveys given to 41 patients who had undergone excision of vaginal mesh placed for treatment of POP. Only 54% reported successful outcomes after mesh excision, with only 3 of 23 patients reporting resolution of dyspareunia. The authors found that patients who had complete excision of mesh, new overactive bladder symptoms after mesh placement, and a body mass index higher than 30 kg/m2 were more likely to report improvement. Blaivas *et al*[26] reported patient improvement after surgical intervention in 47 women with associated mesh-complications. Surgical procedures included sling incision, sling excision, urethrolysis, urethral reconstruction, ureteroneocystoscomy, cystectomy and urinary diversion, and enterocystoplasty. With a median follow up of 2 years (range 0.25 to 12, mean 3), successful outcome was achieved in 34 of 47 patients (72%) after the initial salvage surgery.

In 2015, Rogo-Gupta *et al*[27] reported outcomes of a large series of women, all of whom had undergone removal of synthetic or biological implants between 2005 and 2012. Of the 306 patients, 57% underwent removal for extrusion or erosion, 46% for pain, and 54% for urinary symptoms or incontinence. Twenty-nine percent of had previous revision. Eleven percent of had POP implants, 48% had sling implants, and 41% had both. Seventy-eight percent of the population with pain reported improvement, 14% had worsening of pain, and 9% reported no change. Overall quality of life significantly improved for those who underwent removal of POP and sling implants, and sling implants alone; however, this was not the case for those with only POP implant removal.

Over the last five years, our group has performed over 1200 surgical procedures to remove pelvic mesh (implanted for all indications - including urinary incontinence and POP), in the setting of vaginal bleeding, dyspareunia, and recurrent urinary tract infections (UTIs) with associated mesh extrusion/erosion, in addition to persistent groin and pelvic pain, which only began after mesh implantation. This has provided a robust experience in patient recovery after mesh explantation. Reflecting an oft capitulated concern of worsening incontinence in the setting of mesh removal, we sought to objectively quantify the rate of recurrent urinary incontinence and progression to another anti-incontinence surgery. A portion of this research was recently presented by Ramart *et al*[28] at the International Continence Society (ICS) 2015 Annual Meeting, entitled “Urinary Incontinence After Suburethral Mesh Removal Requiring Anti-Incontinence Procedures”. The research summarizes a retrospective review of 117 continent patients who underwent mid-urethral sling removal for mesh associated complications, most commonly of which was persistent vaginal/pelvic pain [70 retropubic mid-urethral slings (RPMS) and 47 transobturator mid-urethral slings (TOMS)]. At one-year follow up, 38.6% of the RPMS and 34% of TOMS had recurrent SUI requiring an anti-incontinence procedure. Thus, in an initially continent population, post-mesh-removal, approximately one-third of patients progressed to an anti-incontinence procedure within one year.

**ONGOING MATERIALS SCIENCE RESEARCH**

The host response to implanted biomaterials is a series of events that could potentially impact overall tissue functionality and contribute to or even detract from clinical outcomes. As researchers look at materials design, there is now a body of research examining the ability to modulate host-response to implanted synthetic grafts in animal models. For instance, work by Nohuz *et al*[29] has investigated the use of hyaluronate carbxymethylcellulose-based bioresorbable membrane and auto-cross-linked polysaccharide hyaluronan-based solution to prevent polypropylene shrinkage in a rat model; there was significantly less shrinkage of mesh (19.12% and 17%) with the application of these materials compared to a control with a median mesh shrinkage of 29% (*P*-values < 0.05)[28]. The strategy of augmenting the synthetic mesh with an overlying layer or coating is not new. In 2014, Rudnicki *et al*[30] reported their outcomes after implanting collagen-coated mesh for cystocele, comparing it with a conventional anterior colporrhaphy. Although the objective cure rate was significantly improved in the collagen-coated mesh repairs, it was associated with a high exposure rate (13.3%) and no difference in quality of life or sexual function on administered questionnaires, compared to conventional repair. Lo *et al*[31] also reported a notable rate of mesh exposure, 15%, during following up after implantation of collagen-coated mesh for anterior repair.

In 2014, Wolf *et al*[32] investigated the ability to manipulate macrophage polarization following mesh implantation. They performed spatiotemporal analysis of macrophage polarization in response to uncoated polypropylene mesh and mesh coated with hydrated and dry forms of extracellular matrix (ECM) hydrogels derived from either dermis or urinary bladder. The authors concluded that ECM coatings attenuate the pro-inflammatory M1 macrophage response and reduce the number of foreign body giant cells to polypropylene mesh in vivo. With the goal of contributing to the development of synthetic implants that minimize surface area interface and increase integration with host tissue long-term, Faulk *et al*[33] investigated the effects of an ECM hydrogel coating on the long-term host tissue response to propylene mesh in a rodent model of abdominal muscle injury. At 14 d post implantation, the ECM coated polypropylene mesh devices showed a decreased inflammatory response as characterized by the number and distribution of M1 macrophages around mesh fibers when compared to the uncoated mesh devices. At 180 d, the ECM coated polypropylene showed decreased density of collagen and amount of mature type I collagen deposited between mesh fibers when compared to the uncoated mesh devices. The authors concluded this work confirmed and extended the previous findings that an ECM coating mitigates chronic inflammatory response and associated scar tissue deposition. Dias *et al*[34] have examined the use of highly purified collagen gel coating in the immune-inflammatory response, host collagen metabolism, and angiogenesis around propylene mesh in a Wistar rat model. Using 20 Wistar rats, monofilament polypropylene mesh was implanted on one side of the abdominal wall and on the other side a mesh coated with a new highly purified collagen gel was implanted. Sacrificing the animals at 7, 14, 21, and 90 d, multiple assays were performed, including immunohistochemical analysis using interleukin 1 and surface antigen CD-31. The authors concluded that purified collagen coating can impact angiogenesis and the immune reaction of metalloproteinase around mesh implants in rats. This knowledge could contribute to the design of future synthetic grafts used in pelvic floor surgery.

At the 36th Annual Scientific Meeting of AUGS, in October 2015 in Seattle, Washington, Hachim *et al*[35] presented their paper, “Effects of Aging Upon the Host Response to Polypropylene Mesh,” in which they sought to define the effects of aging upon the host response to polypropylene mesh, with particular emphasis on the participation of macrophages. After implanting mesh subcutaneously in young mice (6-8 wk old) and aged mice (18-20 mo old), implants were harvested at delayed time points and host response examined with multiple assays including histologic staining, along with subsequent in vitro studies to investigate the impact of ECMs on observed macrophage phenotype. The authors concluded that the results suggest differences in the character of the host macrophage response to mesh in aged animals, with possible effects upon downstream integration of implants, finding that the host response appears to be a function of at least both cell-intrinsic defects and the local ECM microenvironement.

As did Hachim *et al*[35] (previously described), Mellano *et al*[36] presented their work entitled: “The role of bacterial biofilms and chronic inflammation in the delayed development of pain following transvaginal placement of mesh slings for incontinence,” in October 2015, at the 36th Annual Scientific Meeting of AUGS. The authors examined the possibility of delayed-onset pelvic pain being attributable to bacterial seeding of mesh implanted transvaginally; they described findings from a cohort of women whom reported new onset pelvic pain at least 6 mo after synthetic mesh placement. The study included 20 patients, 18 with delayed-onset pelvic pain and 2 controls (patients with urinary obstruction, no pelvic pain), whom had surgically-removed mesh examined for the presence of bacterial species by polymerase chain reaction-based amplification of bacterial ribosomal RNA (rRNA). Bacterial rRNA transcipts were present in all patients with delayed onset pelvic pain, but not present in the patients with urinary obstruction (no pain). The bacterial species identified were different from vaginal flora cultured at the time of mesh removal (reducing the likelihood the findings were secondary to a contaminated field). The authors concluded that unavoidable colonization of vaginal mesh at the time of transvaginal mesh placement may result in a bacterial biofilm that could contribute to possible delayed-onset pain, through a yet to be characterized mechanism.

**CONCLUSION**

When introduced into the practices of pelvic floor surgeons, the promise of synthetic mesh was outcomes more durable than biologics and native tissue repairs. Recently, Kenton et al reported 5 year outcomes of women enrolled in an observational cohort study after having completed the Trial of Mid-urethral Slings (TOMUS) study[37]. The primary outcome, treatment success, was defined as no re-treatment or self-reported SUI symptoms. At 5 years, this was 51.3% in women assigned to the retropubic sling and 43.4% in women assigned to the transobturator sling; contrary to previously held beliefs, just as with biological materials, permanent mesh slings showed a progressive decrease in efficacy over time.

Thus, one has to ask - does the field of pelvic medicine and reconstructive surgery really need polypropylene mesh? Withagen *et al*[38] reported findings from their randomized control trial examining conventional vaginal repair (97 women) *vs* repair with trocar-guided tension free vaginal mesh (93 women), in a population with recurrent prolapse. Twelve mo after surgery, anatomic treatment failure in the treated compartment was observed in 45.2% of the conventional group and 9.6% of the mesh group (*P* < 0.001); subjective improvement was reported in 80% of the conventional group and 81% in the mesh group. Mesh exposure was detected in 16.9% of the mesh repair patients. This is just an example of how important it is to understand that curing the anatomy is not the most important factor for patients’ perceptions of success; the subjective outcomes are the same in both arms of this trial. However, the after-effects of mesh-associated complications (and 16.9% of this group had mesh exposure within 12 mo) can linger with patients for years potentially.

While the previously described literature represents advances in biomaterials science and the ability to impact host-response in animal models, it is not known if this body of knowledge will translate into clinically meaningful and relevant alterations in the design of future synthetic grafts utilized (*i.e*., would modifications ultimately impact patients long-term outcomes). While mesh augmented prolapse repair would appear to improve anatomical outcomes, this does not consistently translate into improved patient satisfaction and subjective outcomes. The use of mesh implantation has to be balanced with the added morbidity of possible delayed mesh extrusion/erosion over-time. The future of POP surgical repair may very well be in new, more durable biologics, completely moving beyond any continued use of synthetic materials.

In an opinion-piece in 2013, Drs. Chapple, Raz, Brubaker, and Zimmern noted that although mesh insertion may seem like an easy procedure, treating complications of mesh surgery may require extensive and complex procedures; even with mesh removal, it is possible that more than 30% of patients may be permanently disabled or experience long-term symptoms[39]. The full scope of patients requiring reoperation in the setting of previous mesh placement may still be largely unknown, as the presentations can occur years later, as women age and post-menopausal status impacts on tissue quality compound. Thus, there is a subset of the patient population that will have mesh-associated complications, some of whom will benefit from surgical revision and a portion of whom will not. The work presented by Ramart *et al*[28] at the recent ICS Annual Meeting provides an objective assessment of progression to additional anti-continence surgery with 1 year of sub-urethral mesh removal (approximately 1/3 of patients). Determining what makes an individual more at-risk for any of the myriad of mesh-associated complications and ameliorating any such risk is the subject of ongoing research efforts. It should be underscored that this review is not a critique of the use of mesh in pelvic surgery. Our national organizations, AUGS and the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU), have put forth well-written statements endorsing the safety of the polypropylene mesh mid-urethral sling for SUI[40]. We simply seek to recognize that there will be women who will suffer from complications after these implants (just as there can be complications and poor outcomes after any type of surgery), and it is important to recognize the need and possible benefit of effective intervention, all the while continuing to challenge ourselves to improve the techniques and materials we use in pelvic reconstruction.

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**Table 1 Presentation of mesh-associated adverse outcomes**

|  |  |
| --- | --- |
| Possible patient risk factors | Possible patient complaints |
| Prior pelvic surgery  Chronic steroid use  Auto-immune disorders  Factors mitigating wound healing  Smoking  Significant vaginal atrophy  Concomitant hysterectomy  Certain mesh types  Early resumption of intercourse | Dyspareunia  Hispareunia  Worsened urinary incontinence  *De novo* urinary urgency  Urinary retention  Vaginal pain/scarring  Vaginal bleeding/discharge  Recurrent UTIs  Secondary prolapse  Suprapubic pain  Groin/lower extremity pain  Defecatory dysfunction |

UTIs: Urinary tract infections.